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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,987	03/13/2001	Christian Waeber	M0765/7035 (ERG/MAT)	9309

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EXAMINER	
LI, RUIXIANG	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,987	WAEBER ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *89,97,109,132,135 and 138* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,43,56,88, 90, 91,93,96, 98, 99,101-105,108, 110, 111,113,114,121-131,134,137,and 140-148* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/31/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

The Request filed on March 1, 2004 for Continued Examination (RCE) under 37 CFR 1.114 of Application 09/804,987 is granted. An action on the RCE follows.

Applicants' Amendment and Claims

Applicants' amendment filed on December 31, 2003 has been entered. Claims 34, 43, 56, 88-91, 93, 96-99, 101-103, 108-111, 113, 114, 121, 124, 127, 130-132, 134, 135, 137, and 138 have been amended. Claims 140-148 have been added. Claims 34, 43, 56, 88-91, 93, 96-99, 101-105, 108-111, 113, 114, 121-132, 134, 135, 137, 138, and 140-148 are pending. Claims 34, 43, 56, 88, 90, 91, 93, 96, 98, 99, 101-105, 108, 110, 111, 113, 114, 121-131, 134, 137, and 140-148 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objection

The rejection of claim 104 under 35 U.S.C. §112, 1st paragraph for written description, and the rejection of claim 104 under 35 U.S.C. §112, 2nd paragraph,

as set forth in Paper No. 14 & 17, have been withdrawn in view of Applicants' argument.

Information Disclosure Statement

The information disclosure statement filed on December 31, 2003 has been considered by the Examiner and a signed copy of the substitute form PTO-1449 is attached to the office action.

It is noted, however, the information disclosure statement filed on January 20, 2004, which discloses a reference (the International Preliminary Examination Report PCT/US01/08123), fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. In order for the reference to be officially considered, a PTO-1449 form (or modified form) must be provided.

Claim Rejections Under 35 U. S. C. § 112, 1st Paragraph (Scope of Enablement)

The rejection of claims 34, 43, 56, 88, 90, 91, 93, 96, 98, 99, 101-105, 108, 110, 111, 113, 114, 121-131, 134, and 137 under 35 U. S. C. § 112, 1st paragraph for scope of Enablement, as set forth in the previous office actions (Paper No. 14 and Paper No. 17) is maintained. New claims 140-148 are also rejected under 35 U. S. C. § 112, 1st paragraph on the same basis.

Beginning at page 11 of the amendment filed on December 31, 2003, Applicants continue to argue (i) that Applicants' data clearly demonstrates EDG-3 involvement but is not preclude the involvement of other EDG receptors in S1P-induced vasoconstriction; (ii) that the antisense experiment says nothing of EDG-5 involvement in vasoconstriction; and (iii) others have shown that EDG-5 is involved in vasoconstriction. This has been fully considered, but is not deemed to be persuasive for the reasons set forth at the 2nd paragraph of page 5 to top of page 7 of the previous office action (Paper No. 17, August 26, 2003).

Beginnin at page 12 of the amendment filed on December 31, 2003, Applicants continue to argue that based upon the guidance and working examples provided by the specification, one of ordinary skill is able to make, screen and use further EDG receptor inhibitors. Applicants submit that the specification provides examples of EDG receptor inhibitors and methods for screening agents to be used in the claimed methods and identifies WO 99/35259 and WO 99/46277 as teaching methods for making and identifying EDG receptor antagonists. Applicants further argue, citing case law, that the level of skill in the art at the time the instant case was filed was high, and undue experimentation is not required to practice the claimed methods.

This has been fully considered, but is not deemed to be persuasive for the following reasons, as well as for the reasons set forth at the 3rd paragraph of page 7 to top of page 8 of the previous office action (Paper No. 17, August 26,

2003). The claims recite a genus of EDG (or EDG-3) receptor inhibitors, but the specification only discloses two EDG-3 receptor inhibitors, sphingosine and suramin, which have different structures. The disclosed Rho pathway inhibitors HA1077 and Y27632 have not been shown to act as EDG-3 receptor inhibitors and to inhibit EDG-3 receptor signaling. The specification fails to disclose any characteristic structure for the claimed genus of inhibitors. The specification does not provides sufficient guidance or working examples in this unpredictable art, and thus one skilled in the art would have been unable to prepare the claimed genus of EDG (EDG-3) receptor inhibitors. Furthermore, the instant disclosure and WO 99/35259 and WO 99/46277 only teach a method of screening or identifying EDG receptor antagonists, do not teach how to make the genus of EDG (or EDG-3) receptor inhibitors. It is noted that an assay for screening or identifying a product is not equivalent to a positive recitation of how to make a product. Therefore, without the disclosed particular structure of the claimed genus of EDG receptor inhibitors, without sufficient guidance or working examples, one skilled in the art would take undue experimentation to make the EDG (or EDG-3) receptor inhibitors and to practice the claimed methods.

Beginnin at the bottom of page 13 of the amendment filed on December 31, 2003, Applicants continue to argue (i) that the specification teaches that sphingosine-1-phosphate (S1P) induces vasoconstriction in cerebral and coronary arteries; (ii) the specification provides data in Table 1 that show the contractile response in coronary arteries to S1P; (iii) that supplemental figure 1

shows the vasoconstrictive effects of S1P on coronary arteries in rats; and (iv) that the vasoconstrictive effects of S1P in arteries other than cerebral arteries have been confirmed by others.

This has been fully considered, but is not deemed to be persuasive for the following reasons, as well as for the reasons set forth at the bottom of page 3 to top of page 5 of the previous office action (Paper No. 17, August 26, 2003). The data in Table 1 shows that S1P induced 16.9% of the contractile response to KCL in coronary arteries, compared with 96.7% and 77.6% of the contractile response to KCL in Basilar and middle cerebral arteries. Based upon these results, Applicants concluded, in the sections of Summary of the Invention and Examples, that S1P is able to cause the selective constriction of cerebral arteries such as the basilar artery and middle cerebral artery, but not normal peripheral arteries such as the femoral, carotid or coronary arteries (lines 25-29 of page 2; lines 13-14 of page 54). Applicants cannot ignore the instant disclosure and argue against the specification. Even applicants' own publication (Eur. J. Pharmacol. 2003 May 23;469(1-3):125-34) after filing date teaches that S1P selectively constricted isolated cerebral, but not peripheral arteries. Since the invention is drawn to a method of treatment with an agent that increases vasodilation or inhibition vasoconstriction, the claimed invention treating any arteries other than cerebral artery was enabled at the time the instant application was filed. It is noted that the examiner is not able to examine the validity of the data presented in the supplemental Figure 1 because the conditions under which

the experiments were carried out are not described and the data is not submitted in a appropriate form. In addition, the art cited by the applicants does not enable the instant invention. According to the Wands factors, the state of the art, the relative skill of those in the art, and the predictability or unpredictability of the art are all considered at the time when the instant application was filed, i.e., the effective filing date of the application. The art after the filing date of the application does not provide supporting evidence that the claimed invention was enabled at the time the instant application was filed.

Claim Rejections Under 35 U. S. C. § 112, 1st Paragraph (Written Description)

Claims 34, 43, 56, 88, 90, 93, 96, 98, 101-105, 108, 110, 113, 114, 121-131, 134, and 137 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 34, 43, 56, 88, 90, 93, 96, 98, 101-105, 108, 110, 113, 114, 121-131, 134, and 137 are drawn to a method for treating a subject having, or at risk of having, a disorder which can be treated by increased cerebral or coronary vasodilation or inhibition of cerebral or coronary vasoconstriction, comprising administering to a subject in need of such treatment an agent that down-regulates EDG receptor signaling to treat the disorder, wherein EDG receptor signaling is EDG-3 or EDG-5 receptor signaling and wherein *the agent is an EDG receptor inhibitor or an EDG-3 receptor inhibitor*. The claims do not require that EDG receptor inhibitor or an EDG-3 receptor inhibitor possesses any particular conserved structure or disclosed distinguishing feature. In view of the instant disclosure, and Applicants argument (the middle of page 12) filed in the amendment dated on December 31, 2003 that the specification defines EDG receptor inhibitors as agents that decrease the level of EDG receptors at either the mRNA or protein level, agents that interfere with EDG receptor signaling (e.g., by preventing EDG receptor binding to an agonist such as a naturally occurring ligand, or interfering with a downstream factor required for EDG receptor signal transduction), the instant claims encompass a genus of EDG/EDG-3 inhibitors, which have diversified structures and properties.

However, the instant disclosure does not adequately support the scope of the claimed genus. The instant disclosure fails to provide sufficient description information, such as definitive structural features of the claimed genus of

inhibitors. There is no defined relation between function and structure of the inhibitors. The specification merely discloses of EDG-3 receptor inhibitors, sphingosine and suramin, which are not representatives of the genus of the inhibitors recited in the methods of the present invention. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed inhibitors as being identical to those instantly claimed. It is noted that mere assertion of what a compound does without disclosure of the chemical structure of the compound is not sufficient to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of inhibitors.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of the inhibitors. Therefore, only the method of treating a disorder comprising administering the specific EDG-3 inhibitors (sphingosine and suramin) disclosed in the specification, but not the full

breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections Under 35 U. S. C. § 112, 2nd Paragraph

Claims 140-148 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: "administering to a subject in need of such treatment an EDG-3 receptor inhibitor in an amount effective to treat the disorder, wherein the inhibitor is selected from ...". Such a step of administering is essential for practicing the method of the present invention.

Claim Objections—Minor Informalities

Claims 34, 43, 56, 88, 93, 96, 101-105, 108, 113, 114, 121-131, 134, and 137 are objected to because they recite non-elected EDG receptor inhibitors.

Newly added claims 140-148 are objected to because they encompass a method for treating a subject having, or at risk of having, a disorder which can be treated by increased vasodilation or inhibition of vasoconstriction comprising administering to a subject in need of such treatment a sphingosine kinase inhibitor or a sphingosine-1-phosphate phosphatase activator, which are non-elected subject matter (see the election/restriction requirement set froth in Paper No. 11). Appropriate correction is required.

The Examiner notes that the objection will be maintained during the process of prosecution on the merits of elected species.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. The fax number for this Group is (703) 872-9306.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim

Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Ruixiang Li

Ruixiang Li, Ph.D.
Examiner
May 2, 2004

Continuation of Disposition of Claims: Claims pending in the application are 34,43,56,88-91,93,96-99,101-105,108-111,113,114,121-132,134,135,137,138 and 140-148.